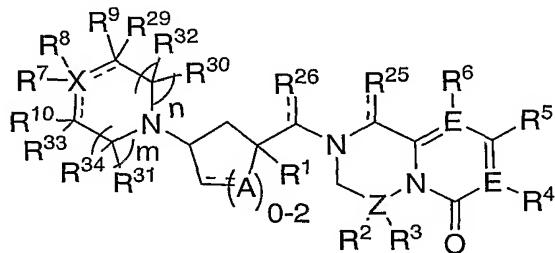
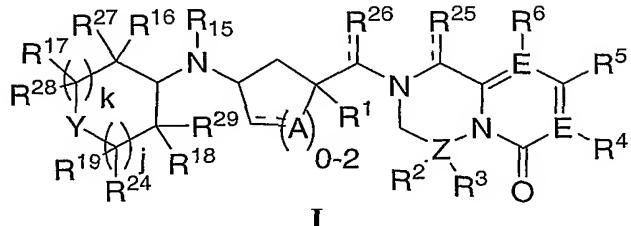


WHAT IS CLAIMED IS:

1. A compound of Formula I or Formula II:



wherein:

A is selected from: -CH₂-, -O-, -N(R²⁰)-, -S-, -SO-, -SO₂-, -N(SO₂R¹⁴)-, and -N(COR¹³)-;

E is independently selected from N and C;

15

X is O, N, S, SO₂ or C;

Y is selected from: -O-, -N(R²⁰)-, -S-, -SO-, -SO₂-, and -C(R²¹)(R²²)-, -N(SO₂R¹⁴)-, -N(COR¹³)-, -C(R²¹)(COR¹¹)-, -C(R²¹)(OCOR¹⁴)- and -CO-;

20

Z is selected from C, N or O;

R¹ is selected from: hydrogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -SO-C₁₋₆alkyl, -SO₂-C₁₋₆alkyl, -SO₂NR¹²R¹², -NR¹²-SO₂-NR¹²R¹², -(C₀₋₆alkyl)-(C₃₋₇cycloalkyl)-(C₀₋₆alkyl), -CN, -NR¹²R¹², -NR¹²COR¹³, -NR¹²SO₂R¹⁴, -COR¹¹, -CONR¹²R¹², -NR¹²CONR¹²R¹², -O-CO-C₁₋₆alkyl, -O-CO₂-C₁₋₆alkyl, hydroxy, heterocycle and phenyl,

where said alkyl and cycloalkyl are unsubstituted or substituted with 1-7 substituents independently selected from: halo, hydroxy, -O-C₁₋₆alkyl unsubstituted or substituted with 1-6 fluoro, C₁₋₆alkyl unsubstituted or substituted with 1-6 fluoro, -CONR¹²R¹², -NR¹²CONR¹²R¹², -COR¹¹, -SO₂R¹⁴, -NR¹²COR¹³, -NR¹²SO₂R¹⁴, -heterocycle, =O, -CN, phenyl, -SO₂NR¹²R¹², -NR¹²-SO₂-NR¹²R¹², -S-C₁₋₆alkyl unsubstituted or substituted with 1-6 fluoro, -SO₂-C₁₋₆alkyl, unsubstituted or substituted with 1-6 fluoro, and -O-COR¹³,

5

where said phenyl and heterocycle are unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, -COR¹¹, C₁₋₃alkyl, and C₁₋₃alkoxy, said C₁₋₃alkyl and C₁₋₃alkoxy being unsubstituted or substituted with 1-6 fluoro;

10

R² and R³ are nothing when Z is O;

15 R² is nothing and R³ is hydrogen or C₁₋₃alkyl when Z is N;

R² and R³ are independently hydrogen or C₁₋₃alkyl unsubstituted or substituted with 1-3 fluoro, when Z is C;

20 R⁴ is selected from: hydrogen, C₁₋₃alkyl unsubstituted or substituted with 1-3 fluoro, -O-C₁₋₃alkyl unsubstituted or substituted with 1-3 fluoro, hydroxy, chloro, fluoro, bromo, phenyl and heterocycle, when E is C;

25 R⁵ is selected from: fluoro, chloro, bromo, -heterocycle, -CN, -COR¹¹, C₄₋₆cycloalkyl, -O-C₄₋₆cycloalkyl, C₁₋₆alkyl unsubstituted or substituted with 1-6 fluoro or hydroxyl or both, -O-C₁₋₆alkyl unsubstituted or substituted with 1-6 fluoro, -CO-C₁₋₆alkyl unsubstituted or substituted with 1-6 fluoro, -S-C₁₋₆alkyl unsubstituted or substituted with 1-6 fluoro, -pyridyl unsubstituted or substituted with one or more substituents selected from halo, trifluoromethyl, C₁₋₄alkyl and COR¹¹, -phenyl unsubstituted or substituted with one or more substituents selected from halo, trifluoromethyl, C₁₋₄alkyl and COR¹¹, -O-phenyl unsubstituted or substituted with one or more substituents selected from halo, trifluoromethyl, C₁₋

30

C_4alkyl and COR^{11} , $-\text{C}_{3-6}\text{cycloalkyl}$ unsubstituted or substituted with 1-6 fluoro, and $-\text{O-C}_{3-6}\text{cycloalkyl}$ unsubstituted or substituted with 1-6 fluoro, when E is C;

5 R^6 is selected from: hydrogen, hydroxy, chloro, fluoro, bromo, phenyl, heterocycle, $\text{C}_{1-3}\text{alkyl}$ unsubstituted or substituted with 1-3 fluoro and $-\text{O-C}_{1-3}\text{alkyl}$ unsubstituted or substituted with 1-3 fluoro, when E is C;

10 R^4 and R^6 are independantly selected from nothing or O (to make an N-oxide) when E is N;
10 R^7 is selected from: hydrogen, $(\text{C}_{0-6}\text{alkyl})\text{-phenyl}$, $(\text{C}_{0-6}\text{alkyl})\text{-heterocycle}$, $(\text{C}_{0-6}\text{alkyl})\text{-C}_{3-7}\text{cycloalkyl}$, $(\text{C}_{0-6}\text{alkyl})\text{-COR}^{11}$, $(\text{C}_{0-6}\text{alkyl})\text{-}(alkene)\text{-COR}^{11}$, $(\text{C}_{0-6}\text{alkyl})\text{-SO}_3\text{H}$, $(\text{C}_{0-6}\text{alkyl})\text{-W-C}_{0-4}\text{alkyl}$, $(\text{C}_{0-6}\text{alkyl})\text{-CONR}^{12}\text{-phenyl}$ and $(\text{C}_{0-6}\text{alkyl})\text{-CONR}^{23}\text{-V-COR}^{11}$, when X is N or C,

15 where W is selected from: a single bond, $-\text{O-}$, $-\text{S-}$, $-\text{SO-}$, $-\text{SO}_2-$, $-\text{CO-}$, $-\text{CO}_2-$, $-\text{CONR}^{12}-$ and $-\text{NR}^{12}-$,

where V is selected from $\text{C}_{1-6}\text{alkyl}$ or phenyl,

20 where R^{23} is hydrogen or $\text{C}_{1-4}\text{alkyl}$, or R^{23} is a 1-5 carbon linker to one of the carbons of V to form a ring,

where said $\text{C}_{0-6}\text{alkyl}$ is unsubstituted or substituted with 1-5 substituents independently selected from: halo, hydroxy, $-\text{C}_{0-6}\text{alkyl}$, $-\text{O-C}_{1-3}\text{alkyl}$, trifluoromethyl and $-\text{C}_{0-2}\text{alkyl-phenyl}$,

25 where said phenyl, heterocycle, cycloalkyl and $\text{C}_{0-4}\text{alkyl}$, if present, are unsubstituted or substituted with 1-5 substituents independently selected from: halo, trifluoromethyl, hydroxy, $\text{C}_{1-3}\text{alkyl}$, $-\text{O-C}_{1-3}\text{alkyl}$, $-\text{C}_{0-3}\text{-COR}^{11}$, $-\text{CN}$, $-\text{NR}^{12}\text{R}^{12}$, $-\text{CONR}^{12}\text{R}^{12}$ and $-\text{C}_{0-3}\text{-heterocycle}$,

30 or where said phenyl or heterocycle is fused to another heterocycle, said other heterocycle being unsubstituted or substituted with 1-2 substituents independently selected from hydroxy, halo, $-\text{COR}^{11}$, and $-\text{C}_{1-3}\text{alkyl}$,

and where alkene is unsubstituted or substituted with 1-3 substituents which are independently selected from: halo, trifluoromethyl, C₁₋₃alkyl, phenyl and heterocycle;

5 R⁷ is absent when X is O, S, or SO₂;

R⁸ is selected from: hydrogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkyl-hydroxy, -O-C₁₋₃alkyl, -COR¹¹, -CONR¹²R¹² and -CN, when X is C;

10 R⁸ is nothing, when X is O, S, SO₂ or N, or when a double bond joins the carbons to which R⁷ and R¹⁰ are attached;

15 or, R⁷ and R⁸ are joined to form a ring selected from: 1H-indene, 2,3-dihydro-1H-indene, 2,3-dihydro-benzofuran, 1,3-dihydro-isobenzofuran, 2,3-dihydro-benzothiofuran, 1,3-dihydro-isobenzothiofuran, 6H-cyclopenta[*d*]isoxazol-3-ol, cyclopentane and cyclohexane,

where said ring is unsubstituted or substituted with 1-5 substituents independently selected from:
halo, trifluoromethyl, hydroxy, C₁₋₃alkyl, -O-C₁₋₃alkyl, -C₀₋₃-COR¹¹, -CN, -NR¹²R¹², -CONR¹²R¹² and -C₀₋₃alkyl-heterocycle;

20 R⁹ and R¹⁰ are independently selected from: hydrogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkyl-COR¹¹, C₁₋₆alkyl-hydroxy, -O-C₁₋₃alkyl, halo;

25 or R⁹ and R¹⁰ together are O, where O is connected to the ring via a double bond;

or, R⁷ and R⁹, or R⁸ and R¹⁰, are joined to form a fused ring which is phenyl or heterocycle, wherein said fused ring is unsubstituted or substituted with 1-7 substituents independently selected from: halo, trifluoromethyl, hydroxy, C₁₋₃alkyl, -O-C₁₋₃alkyl, -COR¹¹, -CN, -NR¹²R¹² and -CONR¹²R¹²;

30 R¹¹ is independently selected from: hydroxy, hydrogen, C₁₋₆alkyl, -O-C₁₋₆alkyl, benzyl, phenyl, C₃₋₆cycloalkyl, where said alkyl, phenyl, benzyl and cycloalkyl groups are unsubstituted or substituted with

1-6 substituents independently selected from: halo, hydroxy, C₁-3alkyl, C₁-3alkoxy, -CO₂H, -CO₂-C₁-6 alkyl, and trifluoromethyl;

R¹² is selected from: hydrogen, C₁-6 alkyl, benzyl, phenyl and C₃-6 cycloalkyl, where said alkyl,
5 phenyl, benzyl and cycloalkyl groups are unsubstituted or substituted with 1-6 substituents independently selected from: halo, hydroxy, C₁-3alkyl, C₁-3alkoxy, -CO₂H, -CO₂-C₁-6 alkyl, and trifluoromethyl;

or, when two separate R¹² groups reside on the same atom or adjacent atoms, said two R¹² groups are
10 optionally connected via a C₁-7alkyl linker to form a 3 to 9 membered ring, said linker being unsubstituted or substituted with 1-6 substituents independently selected from: halo, hydroxy, C₁-3alkyl, C₁-3alkoxy, -CO₂H, -CO₂-C₁-6 alkyl and trifluoromethyl;

R¹³ is selected from: hydrogen, C₁-6 alkyl, -O-C₁-6alkyl, benzyl, phenyl and C₃-6 cycloalkyl, where said alkyl, phenyl, benzyl, and cycloalkyl groups are unsubstituted or substituted with 1-6 substituents independently selected from: halo, hydroxy, C₁-3alkyl, C₁-3alkoxy, -CO₂H, -CO₂-C₁-6 alkyl and trifluoromethyl;

R¹⁴ is selected from: hydroxy, C₁-6 alkyl, -O-C₁-6alkyl, benzyl, phenyl and C₃-6 cycloalkyl, where said alkyl, phenyl, benzyl and cycloalkyl groups are unsubstituted or substituted with 1-6 substituents independently selected from: halo, hydroxy, C₁-3alkyl, C₁-3alkoxy, -CO₂H, -CO₂-C₁-6 alkyl and trifluoromethyl;

R¹⁵ is hydrogen or C₁-6alkyl, where said alkyl is unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, -CO₂H, -CO₂C₁-6alkyl, and -O-C₁-3alkyl;

R¹⁶ is selected from: hydrogen, fluoro, C₃-6 cycloalkyl, -O-C₃-6cycloalkyl, hydroxy, -COR¹¹, -OCOR¹⁴, C₁-6alkyl unsubstituted or substituted with 1-6 substituents selected from fluoro, C₁-3alkoxy, hydroxyl and -COR¹¹, and -O-C₁-3alkyl unsubstituted or substituted with 1-3 fluoro;

or, R¹⁵ and R¹⁶ together are a C₂₋₄alkyl or a C₀₋₂alkyl-O-C₁₋₃alkyl, forming a ring where said ring has 5-7members;

R¹⁷ is selected from: hydrogen, COR¹¹, hydroxy,-O-C₁₋₆alkyl unsubstituted or substituted with 1-6
5 substituents selected from fluoro, C₁₋₃alkoxy, hydroxy, and -COR¹¹ and C₁₋₆alkyl unsubstituted or
substituted with 1-6 substituents selected from fluoro, C₁₋₃alkoxy, hydroxy, and -COR¹¹, or R¹⁷ is
nothing if R²⁸ is connected to a ring carbon via a double bond;

or, R¹⁶ and R¹⁷ together are C₁₋₄alkyl or C₀₋₃alkyl-O-C₀₋₃alkyl, forming ring where said ring has 3-7
10 members;

R¹⁸ is selected from: hydrogen, fluoro, -O-C₃₋₆cycloalkyl, -O-C₁₋₃alkyl unsubstituted or substituted with
1-6 fluoro and C₁₋₆alkyl unsubstituted or substituted with 1-6 fluoro;

15 or, R¹⁶ and R¹⁸ together areC₂₋₃alkyl, where said alkyl is unsubstituted or substituted with 1-3
substituents independently selected from: halo, hydroxy, -COR¹¹, C₁₋₃alkyl, and C₁₋₃alkoxy;

or, R¹⁶ and R¹⁸ together areC₁₋₂alkyl-O-C₁₋₂alkyl, where said alkyl is unsubstituted or substituted with 1-
3 substituents independently selected from: halo, hydroxy, -COR¹¹, C₁₋₃alkyl, and C₁₋₃alkoxy;

20 or, R¹⁶ and R¹⁸ together are -O-C₁₋₂alkyl-O-, where said alkyl is unsubstituted or substituted with 1-3
substituents independently selected from halo, hydroxy, -COR¹¹, C₁₋₃alkyl, and C₁₋₃alkoxy;

25 R¹⁹ is selected from: hydrogen, COR¹¹, SO₂R¹⁴, SO₂NR¹²R¹² and C₁₋₃alkyl unsubstituted or substituted
with 1-6 substituents independently selected from fluoro and hydroxyl;

30 R²⁰ is selected from: hydrogen, C₁₋₆ alkyl, benzyl, phenyl and C₃₋₆ cycloalkyl, where said alkyl,
phenyl, benzyl and cycloalkyl groups are unsubstituted or substituted with 1-6 substituents independently
selected from halo, hydroxy, C₁₋₃alkyl, C₁₋₃alkoxy, -CO₂H, -CO₂-C₁₋₆ alkyl, and trifluoromethyl;

R²¹ and R²² are independently selected from: hydrogen, hydroxy, C₁₋₆ alkyl, -O-C₁₋₆alkyl, benzyl, phenyl and C₃₋₆ cycloalkyl where said alkyl, phenyl, benzyl, and cycloalkyl groups can be unsubstituted or substituted with 1-6 substituents independently selected from: halo, hydroxy, C₁₋₃alkyl, C₁₋₃alkoxy, -CO₂H, -CO₂-C₁₋₆ alkyl and trifluoromethyl;

5 R²⁴ is selected from: hydrogen, COR¹¹, SO₂R¹⁴, SO₂NR¹²R¹² and C₁₋₃alkyl, where said alkyl is unsubstituted or substituted with 1-6 substituents independently selected from: fluoro and hydroxyl; or, R²⁴ and R¹⁷ together are a C₁₋₃alkyl bridge;

10 R²⁵ and R²⁶ are independently selected from: =O where R²⁵ and/or R²⁶ is oxygen and is connected via a double bond, hydrogen, phenyl, and C₁₋₆alkyl substituted or unsubstituted with 1-6 substituents selected from -COR¹¹, hydroxy, fluoro, chloro and C₁₋₃alkyl;

15 R²⁷ is selected from: hydrogen, COR¹¹, SO₂R¹⁴, SO₂NR¹²R¹² and C₁₋₃alkyl, where said alkyl is unsubstituted or substituted with 1-6 substituents independently selected from fluoro and hydroxyl;

20 R²⁸ is selected from selected from: hydrogen, hydroxy, halo, C₁₋₃alkyl unsubstituted or substituted with 1-6 substituents independently selected from fluoro and hydroxy, -NR¹²R¹², -COR¹¹, -CONR¹²R¹², -NR¹²COR¹³, -OCONR¹²R¹², -NR¹²CONR¹²R¹², -heterocycle, -CN, -NR¹²-SO₂-NR¹²R¹², -NR¹²-SO₂-R¹⁴, -SO₂-NR¹²R¹² and =O where R²⁸ is connected to the ring via a double bond and where R¹⁷ at the same position is absent;

25 R²⁹ and R³³ are selected from: hydrogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkyl-COR¹¹, C₁₋₆alkyl-hydroxy, -O-C₁₋₃alkyl, trifluoromethyl and halo, or R²⁹ or R³³ are independently absent if the site of substitution is unsaturated; or, R²⁹ and R¹⁶ together are a C₁₋₃alkyl bridge;

30 R³⁰ and R³¹ are independently selected from: hydroxy, C₁₋₆alkyl, C₁₋₆alkyl-COR¹¹, C₁₋₆alkyl-hydroxy, -O-C₁₋₃alkyl, halo and hydrogen, where said alkyl are unsubstituted or substituted with 1-6 substituents independantly selected from fluoro and hydroxyl;

or, R³⁰ and R³¹ together are a -C₁₋₄alkyl-, -C₀₋₂alkyl-O-C₁₋₃alkyl- or -C₁₋₃alkyl-O-C₀₋₂alkyl-, where said alkyl are unsubstituted or substituted with 1-2 substituents consisting of oxy where the oxygen is joined to the bridge via a double bond, fluoro, hydroxy, methoxy, methyl or trifluoromethyl;

5

R³² and R³⁴ are independently selected from: hydrogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkyl-COR¹¹, C₁₋₆alkyl-hydroxy, -O-C₁₋₃alkyl, trifluoromethyl and halo;

j is 0, 1, or 2;

10

k is 0, 1, or 2;

m is 0, 1, or 2;

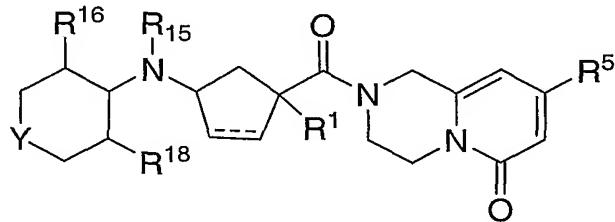
15 n is 1 or 2;

the dashed line represents an optional single bond;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

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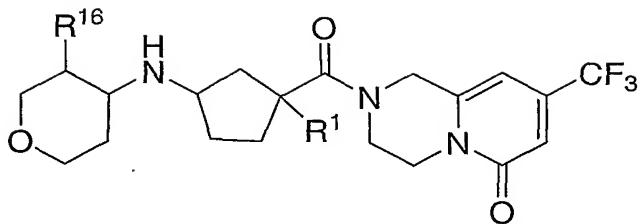
2. The compound of claim 1 of the Formula Ia:



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and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

3. The compound of claim 1 of the Formula Ib:

**Ib**

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

5

4. The compound of claim 1, wherein: A is CH₂, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

10 5. The compound of claim 1, wherein Y is O or CH₂, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

6. The compound of claim 1, wherein E is C, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

15 7. The compound of claim 1, wherein Z is C, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

20 8. The compound of claim 1, wherein R¹ is selected from: -C₁-6alkyl, -C₀-6alkyl-O-C₁-6alkyl, heterocycle, and -(C₀-6alkyl)-(C₃-7cycloalkyl)-(C₀-6alkyl), where said alkyl, heterocycle and cycloalkyl are unsubstituted or substituted with 1-7 substituents independently selected from halo, hydroxy, -O-C₁-3alkyl, trifluoromethyl, C₁-3alkyl, -O-C₁-3alkyl, -COR¹¹, -CN, -NR¹²R¹², -CONR¹²R¹² and -NCOR¹³, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

25 9. The compound of claim 1, wherein R¹ is selected from: C₁-6alkyl, C₁-6alkyl substituted with hydroxy, and C₁-6alkyl substituted with 1-6 fluoro, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

10. The compound of claim 1, wherein R¹ is selected from: -CH(CH₃)₂, -C(OH)(CH₃)₂, -CH(OH)CH₃ and -CH₂CF₃, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

5 11. The compound of claim 1, wherein one or more of R², R³ and R⁴ is hydrogen, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

12. The compound of claim 1, wherein R⁵ is selected from: C₁-6alkyl substituted with 1-6 fluoro, -O-C₁-6alkyl substituted with 1-6 fluoro, chloro, bromo and phenyl, and
10 pharmaceutically acceptable salts thereof and individual diastereomers thereof.

13. The compound of claim 12, wherein R⁵ is trifluoromethyl, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

15 14. The compound of claim 1, wherein R¹⁵ is methyl or hydrogen, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

15. The compound of claim 1, wherein R¹⁶ is selected from: hydrogen, C₁-3alkyl which is unsubstituted or substituted with 1-6 fluoro, -O-C₁-3alkyl, fluoro and hydroxy, and
20 pharmaceutically acceptable salts thereof and individual diastereomers thereof.

16. The compound of claim 1, wherein R¹⁶ is selected from: hydrogen, trifluoromethyl, methyl, methoxy, ethoxy, ethyl, fluoro and hydroxy, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.
25

17. The compound of claim 1, wherein R¹⁷ is hydrogen, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

18. The compound of claim 1, wherein R¹⁸ is selected from: hydrogen, methyl, and
30 methoxy, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

19. The compound of claim 1, R¹⁶ and R¹⁸ together are -CH₂CH₂- or -CH₂CH₂CH₂-, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

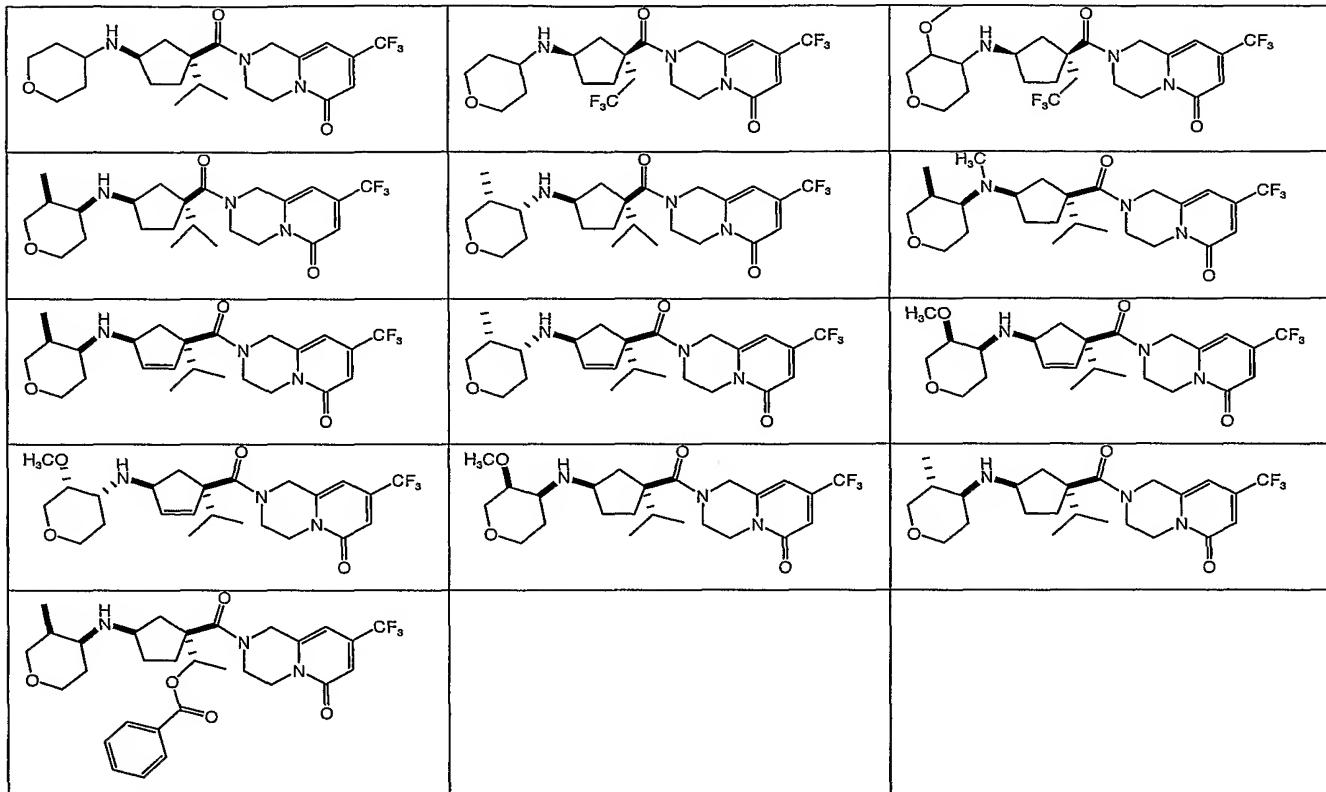
20. The compound of claim 1, wherein one or more of R¹⁹, R²⁴ and R²⁵ is hydrogen,
5 and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

21. The compound of claim 1, wherein R²⁶ is O, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

22. The compound of claim 1, wherein one or more of R²⁷, R²⁸ and R²⁹ is hydrogen, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

23. A compound selected from:

5



and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

24. A pharmaceutical composition which comprises an inert carrier and a compound
10 of Claim 1.

25. A method for modulations of chemokine receptor activity in a mammal which
comprises the administration of an effective amount of a compound of Claim 1.

26. A method for treating, ameliorating, controlling or reducing the risk of an inflammatory and immunoregulatory disorder or disease which comprises the administration to a patient of an effective amount of a compound of Claim 1.

5 27. A method for treating, ameliorating, controlling or reducing the risk of rheumatoid arthritis which comprises the administration to a patient of an effective amount of a compound of Claim 1.